UNITED STAT DEPARTMENT OF COMMER
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/776,044 | 02/26/97 | BYWATER | M 1614-178P |

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| EXAMINER | |
|---|---|
| HOLLERAN, A | |
| ART UNIT | PAPER NUMBER |
| 1642 | |

DATE MAILED: 09/25/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trad marks**

PTO-90C (Rev. 2/95)

*U.S. GPO: 2000-473-000/44602

1- File Copy

| Office Action Summary | Application No. 08/776,044 | Applicant(s) BYWATER ET AL. | |
|---|---|---|---|
| | Examiner Anne Holleran | Art Unit 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Pri rity under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

1. The amendment filed June 27, 2001 is acknowledged.

Claims 1-10, 14 and 15 are pending, and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections Withdrawn:***

3. The denial of priority under 35 U.S.C. 119(a-e) is withdrawn for claim 10 in view of the amendment. The amendment to claim 10, step (a) is interpreted such that step (a) is a step of: determining a nucleotide sequence of all exons encoding biologically functional domains from genomic DNA or cDNA of a cancer-related p53 nucleic acid derived from a human neoplastic tissue or body fluid. Because "biologically functional domains" may be interpreted as domains of a nucleotide sequence that encode the expressed p53 protein and because the specification teaches an example of sequencing exons 2-11, which are the exons that encode the expressed p53 protein, applicant appears to be in possession of one embodiment encompassed by the current recitation of "step a)".

4. The rejection of claim 10 under 35 U.S.C. 112, first paragraph, as containing subject matter that was not disclosed in the original specification is withdrawn in view of the amendment to claim 10.

5. The rejection of claim 15 under 35 U.S.C. 102(e) as being anticipated by Diamandis et al (U.S. Patent No. 5,552,283; issued Sep. 1996; filed Feb. 1995; continuation in part of U.S. Patent 5,545,527, filed July 8, 1994) is withdrawn upon further consideration of the effective filing date of Diamandis et al.

6. The rejection of claims 1-10 and 14 under 35 U.S.C. 103(a) as being unpatentable over Elledge et al (Breast Cancer Res. Treat. 27: 95-102, 1993) and of Callahan (J. Natl. Cancer Institute, 84: 826-827, 1992) in view of Diamandis et al (U.S. Patent No. 5,552,283) is withdrawn upon further consideration of the effective filing date of Diamandis et al.

7. The rejection of claim 2 under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, is withdrawn upon further consideration.

8. The rejection of claim 3 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention is withdrawn in view of the amendment to claim 3.

***Claim Rejections Maintained and New Grounds of Rejection:***

9. The rejection of claims 1-10, 14 and 15 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the following reasons:

Claims 1, 14, 15 are indefinite because of the phrase "all exons of a cancer-related p53 nucleic acid which encode biologically functional domains from genomic DNA or cDNA". The specification confines its teachings to determining the nucleotide sequence of exons 2-11 of a p53 nucleic acid. The remarks by applicant in the response filed June 27, 2001, appear to indicate that phrase "all exons of a cancer-related p53 nucleic acid which encode biologically functional domains" limits the scope of step (a) to a step of determining the entire coding region of a p53 nucleic acid. The confusion lies in the fact that "biologically functional domains" does not structurally define any type of a DNA sequence and is open to interpretation, and also in the fact that the clause "which encode ..." implies that some exons may be excluded from the sequencing step if it were to be determined that a given exon did not encode a "biologically functional domain". It is not clear from the art that all biologically functional domains of a p53 nucleic acid are currently known. Furthermore, dependent claims 4 and 5, are drawn to methods comprising sequencing less than all exons encoding biologically functional domains. Therefore, the scope of claims 1, 14, 15 is unclear. This rejection would be obviated if "step a)" is amended to read "determining the nucleotide sequence of exons 2-11 of a cancer-related p53 nucleic acid derived from a human neoplastic tissue or body fluid;".

Claims 1 and 14 remain indefinite because "step d)" is not adequately correlated with the preamble of the claims. "Step d)" lacks a recitation of how combining the results of steps c) (i) and c) (ii) result in prognostication of the development of neoplasia.

Claim 3 is newly indefinite because the amendment to claim 3 removes a reference to determining the "type" of mutation, but is drawn to a method wherein neoplasia is categorized by biological aggressiveness and/or metastatic potential based upon the presence, position, and type of mutation.

10. The rejection of claim 3 under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, is maintained for the reasons of record.

Applicant's arguments have been considered, but are unpersuasive. Applicant fails to demonstrate that the specification provides a basis to specifically correlate a specific type of mutation (missense, nonsense, deletion, or insertion) of p53 with cancer outcome.

11. The rejection of claim 15 under 35 U.S.C. 102(b) as being anticipated by Thorlacius et al (Thorlacius, S. et al., Cancer Res., 53: 1637-1641, 1993; cited in the IDS) is maintained for the reasons of record.

Applicant appears to argue that "step a)" of claim 15 is limited to determining the nucleotide sequence of the entire coding region of a p53 nucleic acid. However, as discussed above, the wording of "step a)" is confusing and open to interpretation. It is possible to interpret

"step a)" as determining the nucleotide sequence of exons that encode biologically functional domains of a p53 protein. Because Thorlacius teaches sequencing exons 5, 7 and 8, which encode conserved regions of the p53 gene (interpreted as biologically functional domains), it appears that the method of Thorlacius is within the scope of claim 15.

12. The rejection of claims 1, 2, 4-7 and 14 under 35 U.S.C. 103(a) as being unpatentable over Hedrum et al (cited in the IDS and in previous Office Actions) in view of Elledge et al (Breast Cancer Res. Treat. 27: 95-102, 1993) and of Callahan (J. Natl. Cancer Institute, 84: 826-827, 1992) is maintained for the reasons of record. This rejection is newly applied to claims 8-10. Thus, claims 1, 2, 4-10 and 14 stand rejected under 35 U.S.C. 103(a) as unpatentable over the prior art.

Applicant appears to argue that "step a)" of claims 1 and 14 is limited to determining the nucleotide sequence of the entire coding region of a p53 nucleic acid. However, as discussed above, the wording of "step a)" is confusing and open to interpretation. It is possible to interpret "step a)" as determining the nucleotide sequence of exons that encode biologically functional domains of a p53 protein. Because Hedrum teaches a method of analyzing breast tumor samples for p53 mutations in exons 4-9, and teaches sequencing exons 4-9, which are exons that encompass regions that are evolutionarily conserved and also encompass a DNA binding domain, it appears that the sequencing method of Hedrum is within the scope of claims 1, 2, 4-10 and 14.

With respect to the newly made rejection of claim 10, the amendment deleted the reference to the complete coding region of p53 and thus, the amendment necessitated the new

grounds of rejection. Hedrum teaches sequencing using an automated nucleic acid sequencer (see page 121 and Figure 3). With respect to claims 8 and 9, new grounds of rejection are presented. Elledge teaches that patients with breast cancer having a node-negative tumor that contain a p53 mutation have a worse prognosis and a higher risk of relapse (see page 98, 1st column). This teaching indicates and suggests that this subgroup of patients would need adjuvant therapy following surgical removal of the tumor. The therapies recited in claim 9, radiation or chemotherapy/hormone therapy, are standard therapies for breast cancer.

13. Claim 15 is rejected under 35 U.S.C. 102(e) as being anticipated by Vogelstein et al (U.S. Patent 5,527,676; issued June 18, 1996; effective filing date is Dec. 6, 1989).

To the extent that claim 15 may possibly be interpreted to read on a method comprising determining the entire coding sequence of p53 nucleic acid, Vogelstein discloses a method that is the same as that claimed. Vogelstein teaches that mutations of the p53 are associated with the process of tumorigenesis, and that these mutations appear to be associated with a transition from a benign to a malignant state (see column 1, lines 26-47 and column 2, lines 21-26). Vogelstein teaches a method of direct sequencing of the p53 coding region (see Figure 7 and column 3, lines 9-18, and column 13, line 38 – column 14, line 49, and Table 1). Thus, Vogelstein teaches a method of prognosticating the development of neoplasia comprising sequencing and analysis of p53 mutations alone.

14. Claims 1, 2, 4-10 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vogelstein et al (U.S. Patent 5,527,676; issued June 18, 1996; effective filing date is Dec. 6,

1989 in view of Elledge et al (Breast Cancer Res. Treat. 27: 95-102, 1993) and of Callahan (J. Natl. Cancer Institute, 84: 826-827, 1992); and further in view of Hedrum et al (cited in the IDS and in previous Office Actions).

To the extent that claims 1, 2, 4-10 and 14 may possibly be interpreted to read on methods comprising determining the entire coding sequence of p53 nucleic acid, Vogelstein discloses a method for prognosticating the development of a tumor comprising sequencing the entire coding sequence of p53 (see item #13). Vogelstein fails to teach also analyzing the data with respect to node status. However, as discussed previouosly, the teachings of Elledge and Callahan teach that combining the two determinations increases the power of prognosticating the development of tumor. Elledge teaches that patients with breast cancer having a node-negative tumor that contain a p53 mutation have a worse prognosis and a higher risk of relapse (see page 98, 1st column). This teaching indicates and suggests that this subgroup of patients would need adjuvant therapy following surgical removal of the tumor. Vogelstein fails to teach methods of sequencing with automatic sequencers. However, such methods appear to be known in the art as evidenced by the teachings of Hedrum (page 121 and Figure 3). Thus, it would have been prima facie obvious at the time the invention was made to have modified the teachings of Vogelstein to include the assessment of node status as another parameter in a method for prognosticating the development of cancer; it would also have been prima facie obvious at the time the invention was made to have modified the teachings of Vogelstein to use an automatic sequencer to increase the efficiency and speed of the sequencing task.

***Conclusion***

No claim is allowed. This rejection is not made final because of the new grounds of rejection against claims 8, 9 and 15.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
September 18, 2001

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